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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/415 — A1

(11) International Publication Number: WO 96/40122

(43) International Publication Date: 19 December 1996 (19.12.96)

(21) International Application Number: PCT/US96/07445

(22) International Filing Date: 22 May 1996 (22.05.96)

(30) Priority Data:
08/473,817 7 June 1995 (07.06.95) US

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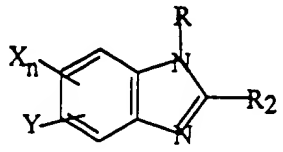
(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: USE OF BENZIMIDAZOLES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF LEUKEMIA

(57) Abstract

A pharmaceutical composition for the treatment of leukemia in mammals is disclosed. The particular fungicide used is a benzimidazole derivative of formula (I), wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen or an alkyl group having from 1 to 8 carbon atoms, and R_2 is 4-thiazolyl or $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms or the pharmaceutically acceptable inorganic or acid addition salts thereof.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
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GA	Gabon			VN	Viet Nam

USE OF BENZIMIDAZOLES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF LEUKEMIA

TECHNICAL FIELD

This invention is a pharmaceutical composition that is useful for the treatment of leukemia, particularly in human and warm blooded animals. The composition contains a benzimidazole derivative.

BACKGROUND OF THE INVENTION

Cancers, including leukemia, are the leading cause of death in animals and humans. The exact cause of leukemia is not known, but links between certain activities such as smoking or exposure to carcinogens and the incidence of certain types of leukemia and tumors has been shown by a number of researchers.

Many types of chemotherapeutic agents have been shown to be effective against leukemia, but not all types of leukemia and tumor cells respond to these agents. Unfortunately, many of these agents also destroy normal cells. The exact mechanism for the action of these chemotherapeutic agents are not always known.

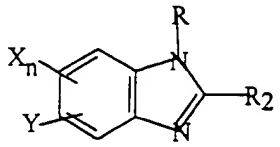
Despite advances in the field of cancer and leukemia treatments the leading therapies to date are radiation and chemotherapy and bone marrow transplants. Chemotherapeutic approaches are said to fight cancers that are particularly aggressive. Such cytocidal or cytostatic agents work best on cancers with large growth factors, i.e., ones whose cells are rapidly dividing. To date, hormones, in particular estrogen, progesterone and testosterone, and some antibiotics produced by a variety of microbes, alkylating agents, and anti-metabolites form the bulk of therapies available to oncologists. Ideally cytotoxic agents that have specificity for leukemia, cancer and tumor cells while not affecting normal cells would be extremely desirable. Unfortunately, none have been found and instead agents which target especially rapidly dividing cells (both diseased and normal) have been used.

Clearly, the development of materials that would target leukemia cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to leukemia cells while exerting mild effects on normal cells would be desirable. Therefore, it is an object of this invention to provide a pharmaceutical composition that is effective in treating leukemia with mild or no effects on normal blood cells

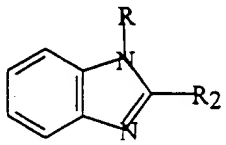
More specifically, it is an object of this invention to provide a composition comprising a pharmaceutical carrier and a benzimidazole derivative as defined herein along with a method for treating leukemia.

SUMMARY OF THE INVENTION

A pharmaceutical composition for treatment of mammals, and in particular, warm blooded animals and humans, which are affected by leukemia comprising a pharmaceutical carrier and an effective amount of a compound selected from the group consisting of:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen, or an alkyl group of from 1 to 8 carbon atoms and R_2 is 4-thiazolyl, $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms, and preferably an alkyl group of less than 7 carbon atoms is claimed. Preferably the compositions are:



wherein R is an alkyl of 1 through 8 carbon atoms and R_2 is selected from the group consisting of 4-thiazolyl, $NHCOOR_1$, wherein R_1 is methyl, ethyl or isopropyl and the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids. The most preferred compounds are 2-(4-thiazolyl)benzimidazole, methyl-(butylcarbamoyl)-2-benzimidazolecarbamate and 2-methoxycarbonylamino-benzimidazole and those wherein Y is chloro.

These compositions can be used to inhibit the growth of leukemia cells in humans or animals by administration of an effective amount either orally, rectally, topically or parenterally, or intravenously. These compositions do not significantly affect healthy cells.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions:

As used herein, the term "comprising" means various components can be conjointly employed in the pharmaceutical composition of this invention. Accordingly, the terms "consisting essentially of" and "consisting of" are embodied in the term comprising.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

As used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the type of mammal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives.

As used herein, a "pharmaceutical addition salts" is salt of the anti-leukemia compound with an organic or inorganic acid. These preferred acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like.

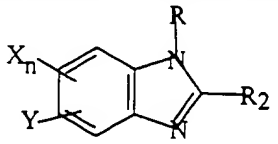
As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the anti-leukemia agent to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

As used herein, "cancer" or "leukemia" refers to all types of cancers or neoplasm or malignant disease which attack normal healthy blood cells or bone marrow which produces blood cells which are found in mammals.

As used herein, the "anti-leukemia compounds" are the benzimidazoles, and their salts. The exact benzimidazoles are described in detail below. The preferred materials are the products sold under the names "thiabendazole®", "benomyl®" and "carbendazim®" by BASF and Hoechst, DuPont and MSD-AgVet.

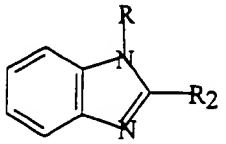
B. THE ANTI-LEUKEMIA COMPOUNDS

The anti-leukemia compounds are benzimidazole derivatives which are known for their antifungal activities. They are systemic fungicides used to prevent and eradicate fungi. The compounds have the following structure:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen or an alkyl group having from 1 to 8 carbons, and R_2 is 4-thiazolyl, $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms, and preferably and alkyl group of less than 7 carbon atoms. Preferably the compositions are:

add benomyl



wherein R is an alkyl of 1 through 8 carbon atoms and R_2 is selected from the group consisting of 4-thiazolyl, $NHCOOR_1$, wherein R_1 is methyl, ethyl or isopropyl and the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids.

add benomyl

The most preferred compounds are 2-(4-thiazolyl)benzimidazole, methyl -(butylcarbamoyl)-2-benzimidazolecarbamate and 2-methoxycarbonylamino-benzimidazole and the compounds wherein Y is chloro and X is hydrogen.

These compounds are prepared according to the method described in U.S. 3,738,995 issued to Adams et al, June 12, 1973. The thiazolyl derivatives are prepared according to the method described in Brown et al., J. Am. Chem. Soc., 83, 1764 (1961) and Grenda et al., J. Org. Chem., 30, 259 (1965).

C. DOSAGE

Any suitable dosage may be given in the method of the invention. The type of compound and the carrier and the amount will vary widely depending on the species of the warm blooded animal or human, body weight, and the type of leukemia being treated. Generally a dosage of between about 2 milligrams (mg) per kilogram (kg) of body weight and about 400 mg per kg of body weight is suitable. Preferably from 15 mg to about 150 mg/kg of body weight is used. Generally, the

dosage in man is lower than for small warm blooded mammals such as mice. A dosage unit may comprise a single compound or mixtures thereof with other compounds or other cancer inhibiting compounds. The dosage unit can also comprise diluents, extenders, carriers and the like. The unit may be in solid or gel form such as pills, tablets, capsules and the like or in liquid form suitable for oral, rectal, topical, intravenous injection or parenteral administration or injection into or around the bone marrow.

D. DOSAGE DELIVERY FORMS

The anti-leukemia compounds are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The active agent can be coadministered in the form of a tablet or capsule, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms would also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in US. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

E. METHOD OF TREATMENT

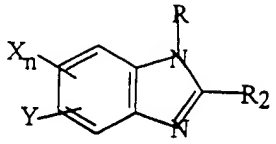
The method of treatment can be any suitable method which is effective in the treatment of the particular leukemia type being treated. Treatment may be oral, rectal, topical, parenteral or intravenous administration or by injection into the bone marrow. The method of applying an effective amount also varies depending on the leukemia being treated. It is believed that parenteral treatment by intravenous, subcutaneous, or intramuscular application of the benzimidazole compounds, formulated with an appropriate carrier, additional cancer inhibiting compound or compounds or diluent to facilitate application will be the preferred method of administering the compounds to warm blooded animals.

The following example is illustrative and is not meant to be limiting to the invention.

Mice are randomly selected and divided into groups for treatment. Five groups are infected with leukemia. The diseased animals are dosed for five days, off two days and then dosed for another five days and then three days off, then dosed for five days and off for two days. This dosing on and off in an irregualr pattern was not an ideal regimien, but the results do show a positive benefit for the Carbendazim™. One group of mice was treated with Cytoxan™, 2-[bis(2-chloroethyl)-amino-1-oxo-2-aza-5-oxophosphoridin, a control was dosed with canola oil and three groups were treated with various levels of Carbendazim™, methyl-(butylcarbamoyl)-2-benzimidazole-carbamate. A control with no treatment was also used. The Carbendazim™ was dosed at three levels 4000 mg/kg, 2500 mg/kg and 1000 mg/kg. The Cytoxan™ was dosed at 125 mg/kg. After 8 days, the no treatment group had lost 1 mouse, by day 10, 8 mice were dead and at day 11 all ten mice were dead. The mice in the Cytoxan™ group survived more than 21 days. The higher dose Carbendazim™ group had one mouse die on day 14, two died on days 15,16 and 17 and one each died on days 20, 21, and 22. The mean number of days for this group is 17.3. The intermediate dosage group had 2 mice die on day 14, 4 on day 15, 1 on day 16, 2 on day 19 and 1 on day 21. The mean number of days for this group is 16.50. The lowest dosage group had 2 mice die on day 12, 13, 14, and 15; and 1 died on each of days 16 and 17. The mean number of days for this group is 14.1.

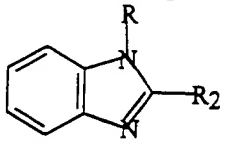
What is Claimed is:

1. A pharmaceutical composition for treating leukemia comprising a safe and effective amount of:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen or an alkyl group having from 1 to 8 carbon atoms, and R_2 is 4-thiazolyl or $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms or the pharmaceutically acceptable inorganic or acid addition salts thereof.

2. A pharmaceutical composition according to Claim 1 comprising a pharmaceutically acceptable carrier and a safe and effective amount of a benzimidazole selected from the group consisting of:



wherein R is hydrogen or an alkyl having from 1 to 8 carbon atoms and R_2 is selected from the group consisting of 4-thiazolyl, $NHCOOR_1$, wherein R_1 is methyl, ethyl or isopropyl and the pharmaceutically acceptable organic or inorganic acid addition salts thereof.

3. A pharmaceutical composition according to Claim 2 wherein said benzimidazole is selected from the group consisting of 2-(4-thiazolyl)benzimidazole, methyl -(butylcarbamoyl)-2-benzimidazolecarbamate and 2-methoxycarbonylamino-benzimidazole.

4. A pharmaceutical composition according to Claim 1, 2 or 3 wherein said pharmaceutical acceptable acid addition salts are selected from the group consisting of chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates and mixtures thereof.

5. A method of treating leukemia in warm blooded mammals comprising administering from 2 mg/kg body weight to 400 mg/kg of a pharmaceutical composition comprising a benzimidazole according to Claim 1, 2, 3 or 4.

6. A method according to Claim 5 wherein said benzimidazole is administered orally or enterically, intravenously, peritoneally, or by injection into the bone marrow.

7. A method according to Claim 5 or 6 wherein said benzimidazole is administered in a liquid form and wherein said liquid dosage from is selected from the group consisting of aqueous solutions, alcohol solutions, emulsions, suspensions, and suspensions reconstituted from non-effervescent and effervescent preparations and suspensions in pharmaceutically acceptable fats or oils.

8. A unit dosage composition for treating leukemia infections in animals or humans comprising a benzimidazole according to Claims 1, 2, 3 or 4.

9. A unit dosage composition according to Claim 8 wherein said benzimidazole is administered in a solid form, wherein said solid form includes a carrier selected from the group consisting of lactose, sucrose, gelatin and agar.

10. A unit dosage composition according to Claim 9 wherein said benzimidazole is administered in a liquid form wherein said liquid dosage from is selected from the group consisting of aqueous solutions, emulsions, suspension solutions, and suspensions reconstituted from non-effervescent and effervescent preparations.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/07445

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THERAPIE, vol. 31, no. 4, 1976, pages 505-515, XP002009247 P.DELATOUR ET AL.: "Propriétées embryotoxiques et antimitotiques en série benzimidazole" see abstract see page 513, paragraph 2 ---	1-10
X	J.NATL.CANCER INST., vol. 74, no. 4, 1985, pages 811-815, XP002009248 SALWA A. EIGEBALY ET AL.: "Reversal of gamma-radiation induced leukemogenesis in mice by immunomodulation with thiabendazole and dinitrofluorobenzene" see abstract see page 811, right-hand column ---	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 1996	13.08.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Tzschoppe, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/07445

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR,A,2 155 888 (AGOT, AIME) 25 May 1973 see claims 1-6 ---	1-4,8,9
X	US,A,3 370 957 (JOSEPH R. WAGNER ET AL.) 27 February 1968 see column 1 - column 4 ---	1-4,8-10
X	J.PEDIATR., vol. 78, no. 1, 1971, pages 129-131, XP002009249 R.J.A.AUR: "Treatment of parasitic infestation in children with malignant neoplasms" see page 129, right-hand column -----	1-4,8

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/07445

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-2155888	25-05-73	NONE		
US-A-3370957	27-02-68	BE-A-	648332	23-11-64
		CH-A-	467020	
		DE-B-	1237731	
		FR-A-	1473828	07-06-67
		GB-A-	1071421	
		NL-C-	134354	
		NL-A-	6405730	24-11-64
		SE-B-	319341	12-01-70

PATENT COOPERATION TRE .Y

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

K. A. DaLack
V. Woof

To:
THE PROCTER & GAMBLE COMPANY
Attn. REED, T. David
5299 Spring Grove Avenue
CINCINNATI, OHIO 45217
UNITED STATES OF AMERICA

KP - Note title Change!

KC: USatty/ECatty/JohH/file

Chile

Applicant's or agent's file reference 5702/SR	Date of mailing *(day/month/year)* 13/08/96
International application No. PCT/US 96/07445	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant THE PROCTER & GAMBLE COMPANY	International filing date *(day/month/year)* 22/05/96

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? To the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2; the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Jennifer Schmitz

Form PCT/ISA/220 (July 1992)

NOTES TO FORM PCT/ISA/220

These notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments wil be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; Claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 TO 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings which cannot be amended under Article 19(1).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confouded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English of French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TRE TY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
5702/SR		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US96/07445	22/05/96	07/06/95

Applicant

THE PROCTER & GAMBLE COMPANY

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

   [ ] filed with the international application.

   [ ] furnished by the applicant separately from the international application,

      [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

   [ ] Transcribed by this Authority

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF BENZIMIDAZOLES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF LEUKEMIA

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/07445

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THERAPIE, vol. 31, no. 4, 1976, pages 505-515, XP002009247 P.DELATOUR ET AL.: "Propriétées embryotoxiques et antimitotiques en série benzimidazole" see abstract see page 513, paragraph 2 ---	1-10
X	J.NATL.CANCER INST., vol. 74, no. 4, 1985, pages 811-815, XP002009248 SALWA A. EIGEBALY ET AL.: "Reversal of gamma-radiation induced leukemogenesis in mice by immunomodulation with thiabendazole and dinitrofluorobenzene" see abstract see page 811, right-hand column ---	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 1996	13.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Tzschoppe, D

Form PCT ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR,A,2 155 888 (AGOT, AIME) 25 May 1973 see claims 1-6	1-4,8,9
X	US,A,3 370 957 (JOSEPH R. WAGNER ET AL.) 27 February 1968 see column 1 - column 4	1-4,8-10
X	J.PEDIATR., vol. 78, no. 1, 1971, pages 129-131, XP002009249 R.J.A.AUR: "Treatment of parasitic infestation in children with malignant neoplasms" see page 129, right-hand column	1-4,8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/07445

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-2155888	25-05-73	NONE		
US-A-3370957	27-02-68	BE-A-	648332	23-11-64
		CH-A-	467020	
		DE-B-	1237731	
		FR-A-	1473828	07-06-67
		GB-A-	1071421	
		NL-C-	134354	
		NL-A-	6405730	24-11-64
		SE-B-	319341	12-01-70